UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,463	12/06/2001	Luis Enrique Fernandez Molina	3035-102	4352

6449 7590 07/28/2008

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
07/28/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/003,463	MOLINA ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-13 and 21-29* is/are pending in the application.

4a) Of the above claim(s) *12,13 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2006 and 06 December 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/23/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed April 23, 2008 in response to the Office Action of October 23, 2007, is acknowledged and has been entered. Claims 1, 3-13, and 21-29 are pending. Previously pending claim 1 has been amended. Claims 2 and 14-20 are canceled. Claims 12, 13, and 21-26 remain withdrawn. Claims 1, 3-11, and 27-29 as drawn to the elected species HER-1, oily adjuvant and polypeptide antigen are currently being examined.

Drawings

2. The drawings submitted 9/19/2006 and 12/6/2001 are objected to because Figures 1 and 5 incorrectly state “ECD-REGFm" where they should state “ECD-EGFRm” for murine epidermal growth factor receptor as disclosed in the specification, p. 22. Figures 1 and 5 also incorrectly state “ACF” when they should state “CFA” according to the specification. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as “amended.” If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary

to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Priority/Oath/Declaration

3. This application claims priority to and Applicants submitted the foreign priority document Cuban Patent Application No. 166/2001, filed on July 12, 2001, however Applicants noted with the foreign document submission dated April 5, 2002, that the Cuban Patent Office has changed the serial number of this Cuban Patent Application from 166/2001 to 167/2001 and Applicants stated: "It is planned to file a substitute declaration to reflect this change." It is noted that no substitute declaration has been submitted to reflect this change. Appropriate correction is required.

Applicants did not address this issue in section 3 of the previous Office Action, hence the appropriate correction is still required.

New Rejection

(necessitated by amendments)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 3-11, and 27-29 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation wherein "**the antigen is not structurally changed**" has no clear support in the specification and the claims as originally filed. THIS IS A NEW MATTER REJECTION.

Applicant points to paragraphs 17 and 21 of the published application to support the newly added claim limitation (p. 6 of Remarks). However, a review of paragraph 17 reveals support for "[0017] The novelty of this invention consists in providing formulations that confer immunogenicity to peptides, polypeptides, proteins, and their corresponding DNA sequences, and target cells of vaccine interest, without the need of structural changes in said antigens, by means of their association with Very Small Size Proteoliposomes (VSSP) from Neisseria meningitidis bacteria, which carry therein innate immunity potent ligands, and gangliosides." A review of paragraph 21 reveals support for "[0021] Additionally, the vaccine compositions described in this invention constitute a solution to the growth factor receptor's immunogenicity problems, and their impact in the treatment of tumors, because said receptors showing tyrosine kinase activity, and the gangliosides which are specifically associated to them in membrane molecular clusters, are simultaneously presented to the host immune system in the context of the red flag signals contributed by the VSSP, and needed to effectively

activate the dendritic cells (DC), and to produce the cross-presentation. These vaccine compositions obviate the use of protein conjugation chemical techniques, which generate new spurious immuno-dominant epitopes, further to the fact that they present its components to the immune system, mimicking the molecular associations in which they naturally occur in tumor cells."

The cited support has been considered but has not been found persuasive because the cited support is not drawn to an antigen that is "not structurally changed." Although [0017] discloses "without the need of structural changes in said antigens," this passage does not support the claimed genus of antigens that are "not structurally changed." It is also noted [0017] discloses "without the need of structural changes in **said** antigens," however, there is no antecedent basis for "said antigens" in paragraph [0017]. Paragraph [0021] also does not disclose or support antigens that are "not structurally changed." The subject matter claimed alters the scope of the invention as originally disclosed in the specification.

New Rejection

(based on new considerations)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 6-11, 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Estevez et al (Vaccine, August 2000, 18:190-197).

The claims are drawn to a pharmaceutical composition that potentiates immunogenicity of low immunogenic antigens comprising (s) one or more low immunogenic antigens, wherein the low immunogenic antigen is a polypeptide and (b) a vaccine carrier consisting of very small size proteoliposomes (VSSPs), wherein the VSSPs are derived from the Outer Membrane Protein Complex (OMPC) of *Neisseria meningitides* wherein gangliosides have been incorporated into the OMPC, wherein the antigen is not structurally changed and is not incorporated into the VSSPs and wherein the vaccine carrier stimulates and potentiates both humoral and cellular responses against the antigen (claim 1), wherein the *Neisseria meningitides* is either a wild type or genetically modified strain (claim 6), wherein the VSSPs are obtained by hydrophobically incorporating the gangliosides into the OMPC (claim 7), wherein the gangliosides are GM3 or their N-glycolylated variations (claim 8), wherein the adjuvant is an oily adjuvant and is Incomplete Freund's Adjuvant (claims 9 and 10), the composition of claim 10 wherein the Incomplete Freund's adjuvant is Montanide ISA 51 (claim 11), and the composition of claim 1 wherein the composition further comprises one or more adjuvants (claim 27).

Estevez et al teach that immunization using VSSPs derived from the OMPC of *Neisseria meningitides* with gangliosides hydrophobically incorporated into the OMPC, resulted in significant levels of T-dependent IgG1, IgG2a and IgG2b (cellular) as well as T-independent IgG3 and IgM (humoral) immune responses, wherein no reactogenicity

was observed when self-gangliosides were used for immunization. VSSP overcame natural tolerance to the low-immunogenic self-antigen gangliosides in an adjuvant-dependent fashion (abstract; p. 196, col. 1; Fig. 4). It is known that serotype proteins, which are the main components of the OMPC, induce proliferation and activation of lymphocytes and lead to secretion of IL-2 (p. 196, 1st column, last paragraph to 2nd column). Estevez et al teach immunization using Incomplete Freund's Adjuvant Montanide ISA 51 with the VSSPs derived from the OMPC of *Neisseria meningitides* and gangliosides incorporated into the OMPC (p. 191, col. 2; Table 1; Fig. 4 and 7). Estevez et al teach that Montanide ISA 51 is preferred because it is less toxic than Incomplete Freund's Adjuvant (p. 191, col. 2). Immunization of mice with VSSPs derived from the OMPC of *Neisseria meningitides* and gangliosides incorporated into the OMPC in combination with Montanide ISA 51 resulted in increased immunoglobulin titers compared to mice immunized with the VSSP composition without Montanide ISA 51 (p. 194, col. 2; Table 1). Estevez et al teach that patients suffering from metastatic breast cancer have been immunized with GM3/VSSP and NGcGM3/VSSP vaccines in Montanide ISA 51 for therapy (p. 196, col. 2).

Although Estevez does not specifically teach that the *N. meningitides* is a wild-type strain, the claimed *N. meningitides* appears to be the same as the prior art *N. meningitides*, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the

burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Given the instant specification does not define a “structurally changed" antigen, the gangliosides taught by Estevez are the same gangliosides expressed in breast cancer patients, hence would not be structurally changed.

Estevez does not teach combining the low-immunogenic gangliosides that are not incorporated into the VSSPs with the GM3/VSSP and NGcGM3/VSSP vaccines.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and one would have been motivated to add unincorporated gangliosides to the GM3/VSSP and NGcGM3/VSSP vaccines taught by Estevez et al in order to provide more antigen to produce an immune response for breast cancer therapy. One of ordinary skill in the art would have a reasonable expectation of success adding free gangliosides to the GM3/VSSP and NGcGM3/VSSP vaccines and stimulating an immune response to them given that Estevez successfully demonstrates that VSSPs increase immunogenicity of the low-immunogenic gangliosides. Although the gangliosides are not incorporated into the VSSPs, given the VSSPs are demonstrated as responsible for the adjuvant effect of the ganglioside immune response, one of skill in the art would have a reasonable expectation of success eliciting an immune response to the free gangliosides in a combined composition with VSSPs.

Relevant Arguments

6. Applicants' arguments drawn to the unexpected result of the adjuvant property of VSSP for EGFR (HER-1) are not applicable the new rejection above that addresses only the low immunogenic antigen ganglioside. Given that VSSPs were already known and demonstrated to provide an adjuvant immune response for incorporated gangliosides (Estevez above), the adjuvant effect for VSSPs or GM3/VSSP and NGcGM3/VSSP vaccines in combination with free gangliosides is reasonably expected, and not a surprising result.

7. All other rejections recited in the Office Action mailed April 23, 2008 are hereby withdrawn in view of amendments and arguments.

8. **Conclusion:** No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Examiner, Art Unit 1642